Osteoporosis in Severe Congenital Neutropenia: Inherent to the Disease or a Sequela of G-CSF Treatment?

To the Editor: Severe congenital neutropenia (SCN; Kostmann's syndrome) is characterized by a maturational arrest of myelopoiesis at the promyelocyte stage. Recombinant human granulocyte colony-stimulating factor (G-CSF) has substantially improved the life expectancy for these patients. But a recent report on a 5-year-old child with SCN, suffering from an osteoporotic collapse of vertebral bodies after 3 years therapy with G-CSF [1], raised the question of whether such a dramatic osteoporotic disease is a sequela of G-CSF treatment or an intrinsic feature of SCN.

We describe a 31-year-old woman with SCN, the diagnosis having been confirmed by bone marrow biopsy and repeated measurements of absolute neutrophil counts (ANC) $<0.5 \times 10^9$/L. Cytogenetics showed a normal female karyotype. The clinical course was characterized by recurrent bacterial infections. In addition, her 7-year-old child now shows ANC $<0.5 \times 10^9$/L. At the age of 30 years, G-CSF treatment was started because of severe would healing complications of a skin ulcer caused by a mosquito bite on the lower leg. The G-CSF starting dosage of 6.7 μg/kg/d was decreased to a current dose of 1.7 μg/kg/day, thereby maintaining ANC at $>2 \times 10^9$/L. Two weeks after therapy was begun, plain radiography showed excessive osteoporosis of the tibia and fibula. In the following months, the same was confirmed for the complete vertebral axis, pelvis, and upper and lower limbs. Bone density, measured in mg calcium/mm^3 by Q-CT, was diminished by 45%. Three months after starting G-CSF therapy, compression fractures of multiple vertebral bodies (T4–T9, T12) were documented; two weeks later, spontaneous femoral fracture occurred. Parameters for bone metabolism, including plasma calcium, phosphate, albumin, 1.25-OH-D_2, osteocalcin, estradiol, and parathyroid hormone, were all within the normal range, except for plasma alkaline phosphatase (AP), which showed increased activity before G-CSF therapy was begun. During G-CSF therapy, AP activity continued to increase involving both bone and liver isoenzymes.

In our patient, G-CSF treatment was administered only for a very short time, suggesting that the excessive osteoporosis was an inherent feature of SCN. Osteoporosis within the context of SCN and G-CSF treatment was first described by Zeidler et al. [2], who reported radiologic signs of osteoporosis for 12/32 (38%) patients; in six of these patients, osteoporosis had been found prior to G-CSF therapy, based on plain radiographs. In a report by Bonilla et al. [3], these results have been extended by enrolling additional patients from two other centers, theraby documenting 15/54 (28%) patients with osteoporosis, again six of these prior to G-CSF therapy. Not a single case of osteoporosis was reported by Dale et al. [4], however, in their phase III study of G-CSF treatment in 123 patients with SCN.

The problem of osteoporosis in SCN should be addressed in a prospective quantitative manner, including Q-CT and parameters of bone metabolism, both before and during G-CSF therapy.

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